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The emergence of a circuit model for addiction

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KEYWORDS :

Drug-addiction, cocaine, synaptic plasticity, metabotropic glutamate receptors, calcium permeable AMPA receptors, optogenetics, mouse models of addiction, deep brain stimulation, treatment.

Abstract

Addiction is a disease of altered behavior. Addicts use drugs compulsively and will continue to do so despite negative consequences. Even after prolonged periods of abstinence, addicts are at risk of relapse, particularly when cues evoke memories that are associated with drug use. Rodent models mimic many of the core components of addiction, from the initial drug reinforcement to cue-associated relapse and continued drug intake despite negative consequences. Rodent models have also enabled unprecedented mechanistic insight, revealing plasticity of glutamatergic synaptic transmission evoked by the strong activation of mesolimbic dopamine, - a defining feature of all addictive drugs - , as a neural substrate for these drug-adaptive behaviors. Cell type-specific optogenetic manipulations have allowed both identification of the relevant circuits and design of protocols to reverse drug-evoked plasticity and to establish links of causality with drug-adaptive behaviors. The emergence of a circuit model for addiction will open the door for novel therapies, such as deep brain stimulation.

Content

GLOSSARY:

AMPA receptor: ionotorpic glutamate receptor defined by its selectivity for alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate.

NMDA receptor: ionotorpic glutamate receptor defined by its selectivity for N-methyl-D-aspartate made of an obligatory GluN1 subunit that assembles with GluN2 or GluN3.

GABA: γ-Aminobutyric acid, an inhibitory neurotransmitter

GHB: γ-hydroxybutyrate, a communly used club drug

DAT: dopamine transporter expressed on the cell membrane for the reuptake of the transmitter from the extracellular space.

VTA: ventral tegmental area, a nucleus at the tip of the brainstem with dopamine projection neurons

RmTg: rostromedial tegmentum, a nucleus adjacent to the VTA made of GABA neurons that inhibit DA neurons.

NAc: nucleus accumbens, a nuclues of the ventral striatum that integrates DA inputs from the VTA and glutamate projections from the prefrontal cortext, the amygdala and the ventral hippocampus.

Behavioral sensitization: a process in which repeated injections of a given dose of cocaine results in the progressive amplification of the locomotor response

Incubation of craving: the observation that cocaine seeking when triggered by re-exposure to drug-associated cues progressively increases over the first 2 months after withdrawal from self-administration of the drug.

Conditioned place preference: a form of conditioning used to measure the motivational effects attributed to the environment in which addictive drugs are administed.

Resistance to punishment test: a behavioral assey whereby a mild electric shock is delivered when the animal self-administres an addictive drug to asses its motivational value.

INTRODUCTION: Clinical definition of addiction

A simple definition of addiction is “compulsive drug seeking and use, despite harmful consequences”(Volkow 2014). Clinically, the American Society for Addiction Medicine defines addiction as "a primary, chronic disease of brain reward, motivation, memory and related circuitry" which is characterised by the “inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response” (American Society of Addiction Medicine 2011). The former simple definition has the appeal that it can be modeled in animals, while the latter more accurately captures the full complexity of the human disease. Moreover, addicts are also subject to aversive feelings, which may lead to negative reinforcement via motivational withdrawal (Koob 2009). Since the focus of the present review is on the neural basis of the disease in rodent models, the emphasis will be on the compulsivity and resistance to punishment.

Despite occasional alarming reports, the overall prevalence of addiction has remained constant during the last decades. What is shifting are the specific substances used. In Western Europe, heroin was the most commonly used addictive drug during the 1980’s; today, heroin use has decreased, but cocaine is on the rise. In the US, particularly outside of the big cities, methamphetamine is the leading drug today. Prescription opioids leading to an epidemic of drug overdose pose an additional threat (Rudd et al 2016). In Asia, recreational opioids have traditionally been the most commonly used drugs and are still number one (World Health Organization 2010).

Based on the US-national comorbidity survey (Kessler et al. 2004), early longitudinal clinical studies clearly demonstrate that only a minority of recreational drug users eventually fulfil the diagnostic criteria for the disease (Wagner & Anthony 2002). This landmark work showed that about 15% of cocaine users develop addiction[1] within 10 years of first cocaine use, the corresponding values were 8% for marijuana users and 12–13% for alcohol users (for alcohol, which is regularly consumed by the large majority of the adult population, prevalence for addiction in Europe is estimated to not exceed 4%, albeit with a strong gender bias (Rehm et al. 2015)). This clearly demonstrates that the majority of people can use even the most addictive of drugs recreationally without ever becoming addicted.

One of the most striking features of drug relapse is its dependence on the environment. Addicts typically relapse in settings associated with prior drug use. Conversely, exposed to a different context, addicts typically find it easier to remain abstinent. Another landmark study demonstrated this effect on heroin addicted Vietnam veterans, who had a significantly higher success rate in rehabilitation programs back home compared to “local” addicts (Zinberg 1986). This remarkable finding was attributed to the fact that for these individuals contextual drug cues were rare and thus relapse less common.

While an attempt of a “general theory” for addiction was greeted with criticism (Piazza & Deroche-Gamonet 2014), much research over the past two to three decades supports the notion of addiction as a brain disease, where pharmacological substances exert their effect by usurping the neural reward system. Contrary to common beliefs, addiction is not a neurodegenerative disease, as neurotoxicity is not a common feature of addictive drugs. Here we will present the preclinical evidence for the dopamine system as a common initial target for all addictive drugs and review the literature on adaptive synaptic plasticity as the addiction trace, which maintains compulsive behaviour despite punishment and other negative consequences.

THE DOPAMINE HYPOTHESIS: still alive and kicking

[1] The original publication uses the term “dependence”, which now is now limited to describe the state defined by the withdrawal syndrome upon abrupt termination of drug exposure.

Addictive drugs constitute a group of chemically diverse pharmacological substances with distinct molecular targets. It is therefore not trivial to assume a common function that would trigger the induction of addiction. Yet accumulating evidence points to the dopamine system as the initial target of all addictive drugs.

The first evidence for involvement of the dopamine (DA) system in the acute rewarding effects of addictive drugs dates back to the 1970's (for a review see Wise 2004) with the report that cocaine self-administration in rats was abolished when lesioning DA neurons, but remained unaffected by a chemical destruction of the noradrenergic neurons (Roberts et al. 1977). Subsequently, a systematic characterization using microdialysis to measure DA after systemic administrations of morphine, methadone, ethanol, nicotine, amphetamine, and cocaine showed strong increases of DA for all of these substances (Di Chiara & Imperato 1988). The transient increases in dopamine were particularly marked in the NAc compared to the caudate nucleus. These studies led to the hypothesis that addiction could arise from increased levels of mesolimbic dopamine, which were both necessary and sufficient to induce the disease (**Figure 1**). This needs to be distinguished from the *DA hypothesis of addiction* that posits changes in *DA signaling* as the cause of adaptive behavior (for a review see Melis et al. 2005).

Challenging the DA hypothesis of drug reward

The DA hypothesis of drug reward has been challenged several times (Nutt et al. 2015). In the late 1990's, the observation that mice lacking the DA transporter DAT (DAT-KO mice) still self-administered cocaine received much attention (Rocha et al. 1998). It took the field a decade to understand the mechanism underlying this observation. In fact, in DAT-KO mice a compensatory re-uptake of DA through other monoamine transporters develops and since these transporters were also inhibited by cocaine, DA still increased with drug exposure even in the absence of DAT. Double and triple monoamine transporter KO mice (Sora et al. 2001) finally paved the way for the definitive experiment showing that self-administration of cocaine, but not amphetamine, was abolished in mice that carried a mutated DAT that no longer binds cocaine, but is otherwise functional (Chen et al. 2006).

The DA hypothesis has also been challenged by the observation that morphine still induced conditioned place preference in DA-deficient mice (Hnasko et al. 2005). However, these animals suffered from severely reduced locomotion and other developmental adaptations, which precluded the testing for later stage drug-adaptive behavior. Early studies also suggested that a major drive for morphine reinforcement originates in the tegmental pedunculopontine nucleus (TPP), a small brain stem nucleus receiving GABA projections from the VTA (Bechara & van der Kooy 1992). According to this model, in naïve animals, the reinforcing effects of opiates would be mediated by VTA GABA neurons projecting to the TPP. Conversely, in opiate-dependent but withdrawn animals, collaterals of the same GABA neurons projecting to VTA DA neurons would mediate the reinforcing effects. Opioids dependence would control the ambient chloride concentration of VTA GABA neurons such that the polarity of the GABAA receptor signalling swaps from inhibitory to excitatory (Laviolette et al. 2002). How this then directs the information to one or the other target remains elusive, as well as the locus of μ-opioid receptors that drives the effect of morphine. It is well established that VTA GABA neurons express these receptors in the somato-dendritic as well the axon-terminal compartment. μOR in the former activate K channels of the GIRK family, while the latter inhibit calcium channels to reduce transmitter release (Lüscher et al. 1997). Therefore a more straight forward model, initially proposed in the 1980's, is the disinhibition of DA neurons by opioids because VTA GABA neurons are shut down (Johnson & North 1992).

Similar disinhibition models have been proposed for gamma-hydroxybutyrate (GHB, Cruz et al. 2004)) and benzodiazepines (Tan et al. 2010), both substances with addiction liability. For the former, the molecular target is the $GABA_B$ receptor, expressed both on GABA and DA neurons of the VTA. However, DA neurons do not express GIRK1, and therefore agonist concentrations an order of magnitude higher are required to half-activate the $GABA_B$ receptor effector channel currents (EC_{50}, Labouèbe et al. 2007). Consequently, there is a concentration window where the main effect of GHB is mediated through VTA GABA neurons, which leads to disinhibition of DA neurons.

Benzodiazepines, which are positive allosteric modulators at $GABA_A$ receptors, cause strong inhibition of VTA GABA neurons by virtue of a cell-type specific expression of receptor subunits (Tan et al. 2010). The $GABA_A$ alpha1 subunit is exclusively expressed in GABA neurons, conferring larger single unit conductance to $GABA_A$ receptors on GABA neurons compared to DA neurons, which express channels made of alpha2/3. Benzodiazepines exacerbate this difference and little transmitter is released from VTA GABA neurons. As a consequence there is no GABA on DA neurons that can be amplifyed, ultimately leading to disinhibition and enhanced release of DA.

The mechanistic classification of addictive drugs

Taken together, three distinct cellular mechanisms suffice to propose a mechanistic classification of addictive drugs (Lüscher & Ungless 2006). There are those drugs that can directly depolarise DA neurons (Nicotine), those that interfere with re-uptake (Cocaine, Amphetamines & Ecstasy) and a third group that leads to disinhibition (Opioids, Cannabis, BZD and GHB). Thus, a comprehensive model is emerging, despite some remaining questions, most prominently how to classify ethanol. There is no doubt that ethanol stimulates DA neurons (Gessa et al. 1985) and increases mesolimbic DA (Di Chiara & Imperato 1988), but the relevant molecular target and the cellular mechanism remain elusive.

Increasing the levels of mesolimbic DA as a common pathway of addictive drugs is in line with the dopamine prediction error hypothesis (for recent reviews see Keiflin & Janak 2015, Schultz 2011). Much experimental evidence indicates that under physiological conditions the phasic activity of VTA DA neurons generates a learning signal when an unexpected reward occurs (Schultz et al. 1997). The “purpose” of this signal would be to promote learning such that reward can again be obtained. Once the reward becomes fully predictable DA neurons will no longer be activated and learning ceases (which makes sense as the behavior is now optimized). The sheer pharmacological power of addictive drugs can override this system, thus generating an inappropriate learning signal that ultimately leads to compulsive drug intake at the expense of all other behavior. In this model, addiction should be considered a “gain-of-function” disease, as it is an excessively strong increase of mesolimbic DA concentration that is at the origin of the behavioral dysfunction.

If this is true, then direct sustained stimulation of these neurons should have similarly reinforcing effects. Several studies using optogenetic approaches appear to confirm this prediction. Pairing an environment with optogenetic stimulation of VTA DA neurons leads to an immediate place preference that persists for several days (Adamantidis et al. 2011, Tsai et al. 2009). Self-stimulation of VTA DA neurons is reinforcing and mice will press several hundred times per hour just to receive burst-activation of DA neurons. That injection of an addictive drug strongly occludes optogenetic DA neuron self-stimulation (Pascoli et al. 2015) is another argument that the same system drives the underlying motivation.

While addictive drugs target DA neurons without distinction, it is probable that specific projections from the VTA contribute more than others to the rewarding and ultimately addictive effects. Circumstantial evidence suggests a crucial role for VTA DA neuron projections to the NAc. It is also possible that a subset of DA neurons may code aversive stimuli (Lammel et al. 2014). If this were the case one might speculate that their strong activation may give rise to adaptations in circuits underlying the proposed « opponent process », recently reviewed elsewhere (Koob 2009). Combining cell type-specificity and projection targeting with optogenetic activators will help to resolve the question of the relative contribution by subpopulations.

DRUG-EVOKED SYNAPTIC PLASTICITY: the trace of drug exposure

By definition, relapse occurs when subjects are off drugs. Any neural substrate conferring the risk to start taking drugs again must therefore be a trace that addictive substances leave behind once they have been cleared from the body. In 2001, a seminal study (Ungless et al. 2001) reported that a single dose of cocaine was sufficient to induce a trace at excitatory synapses onto VTA DA neurons that lasted for about a week, and in 2003 the same group showed that the trace could also be

observed after a dose of morphine, nicotine, alcohol or amphetamines (Saal et al. 2003). These two publications initiated much research on changes in glutamatergic transmission caused by the exposure to addictive substances, a phenomenon called “drug-evoked synaptic plasticity” (Lüscher & Malenka 2011). Drug-evoked synaptic plasticity occurs at many other excitatory synapses of the mesocorticolimbic system and beyond as well as at GABAergic synapses where it can affect the fast (Bocklisch et al. 2013, Liu et al. 2005, Nugent & Kauer 2008) and slow inhibitory postsynaptic current (Padgett et al. 2012). It is beyond the scope to the present review to provide a comprehensive list of all reports of drug-evoked synaptic plasticity. Here we will focus on plasticities in the VTA and the NAc, which are most directly affected by the increase of DA caused by addictive drugs. We will review their mechanism of induction, expression and possible cellular reversal protocols. The epigenetic and transcriptional regulation that are part of the underlying molecular mechanisms are reviewed elsewhere (Kenny 2014, Robison & Nestler 2011).

One shot plasticity in the VTA

In DA neurons of the VTA, particularly in those that project to the NAc, excitatory afferents from the lateral dorsal tegmentum (LDT, a brain stem nucleus) are potentiated for several days, starting hours after the first exposure of the animal to any addictive drug (Lammel et al. 2012). The induction depends on NMDA receptors and D1Rs (Ungless et al. 2001), which are activated when DA neurons become active and release DA from their dendrites. The NMDA receptors that drive the induction are located on DA neurons themselves, since the plasticity is abolished in mice where the obligatory NMDA subunit GluN1 is conditionally removed from DA neurons (Engblom et al. 2008). This finding was confirmed by a sophisticated pharmacological experiment, where a “masked” version of the NMDAR open channel blocker is made cell membrane permeable and then enzymatically activated selectively in DA neurons (Yang et al. 2015). The locus of the relevant D1R has not been fully investigated, but they are most likely expressed on the presynaptic terminals of excitatory afferents. The induction of this form of plasticity is therefore a VTA-autonomous process.

The characterisation of the expression mechanism took many years. Initial work suggested that the potentiation was due to the insertion of additional alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors while the NMDA receptors would remain unaffected (Ungless et al. 2001). This interpretation was based on the observation that the ratio of the amplitude of AMPA-mediated/NMDA-mediated postsynaptic currents was higher then normal, a parameter often used to quantify synaptic strength in the acute brain slice preparation. However, the current model favours a more complex scenario, whereby native AMPA receptors are exchanged for receptors that lack the GluA2 subunit, while conversely canonical NMDA receptors are switched for receptors that contain the GluN3 subunit (Mameli et al. 2011, Yuan et al. 2013).

Canonical NMDA receptors are heteromers made from two GluN1 subunits and two GluN2 subunits, which can be of either the 2A or 2B splice variant (Paoletti et al. 2013). Such receptors do not flux current at negative potentials owing to magnesium block of the pore. When depolarised, the magnesium detaches and the receptors can readily flux calcium. By contrast, heterotrimeric NMDA receptors are assembled from two GluN1, one GluN2 and one GluN3 subunit (Perez-Otaño et al. 2001). Such receptors flux hardly any calcium and are insensitive to magnesium. In the VTA of naive animals, canonical NMDA receptors are present and permable to calcium when depolarised, which is essential for the induction of activity dependent as well as drug-evoked synaptic plasticity. After cocaine exposure, changes in the current-voltage relationship, the sensitivity of subunit specific pharmacology, and the direct visualization of the reduced calcium influx are indicative of the presence of heterotrimeric NMDARs (Yuan et al. 2013). This is confirmed by the observation that this form of drug-evoked synaptic plasticity is absent in GluN3 KO mice.

Calcium permeable AMPA receptors

AMPARs typically contain one or two GluA2 subunits, which through post translational editing exchange a glutamine residue for a larger and polarized arginine residue (Q/R editing) in the pore region (Liu & Zukav 2007, Wolf & Tseng 2012). As a result AMPARs have a linear current-voltage

curve that reverses at 0 mV and are virtually calcium impermeable. In fact, in DA neurons of drug naive adult animals all AMPARs are calcium impermeable (CI-AMPARs). After drug exposure, while the total number of receptors remains constants, a substantial fraction of receptors are exchanged for calcium permeable (CP) ones (Bellone & Lüscher 2006). Since CP-AMPARs also have a higher single channel conductance, this exchange results in a net potentiation of the AMPARs excitatory postsynaptic current (EPSC). The presence of CP-AMPARs is demonstrated by the inwardly rectifying current voltage curve. Moreover, endogenous spermines inhibit the EPSC at positive potentials while specific pharmacological substances, such as Joro-spider toxin or naspm can also block synaptic currents at negative potentials.

Given the dual redistribution of NMDARs and AMPARs, the increased A/N ratio receives a different interpretation. This ratio, when calculated by dividing the amplitudes of the EPSCs measured at +40 mV increases, because the decrease in NMDA current exceeds the partial reduction of the macroscopic AMPA current. The latter is due to the rectification, which yields smaller currents at positive potentials, even if the number of receptors remains identical. Functionally, the switch of the synaptic source of calcium may impact on the induction of activity dependent plasticity (Mameli et al. 2011). In naive animals, afferent activity paired with a depolarization leads to an LTP-like potentiation driven by calcium fluxing through canonical NMDARs. After cocaine exposure, this protocol becomes inefficient, but LTP can be rescued by paring afferent stimulation with the hyperpolarization of the DA neurons, which facilitates the calcium entry through CP-AMPARs. While there is good evidence that such a scenario exists in acute brain slices, no experimental evidence has yet demonstrated the significance of this meta-plasticity *in vivo*.

As already suggested by the initial publications, all addictive drugs tested to date induce this form of drug-evoked synaptic plasticity. Specifically, changes in A/N and/or rectification have been reported for cocaine, amphetamine, nicotine, morphine, heroine, diazepam, midazolam, ethanol and cannabis (Good & Lupica 2010, Heikkinen et al. 2009, Saal et al. 2003, Tan et al. 2010, Ungless et al. 2001). The orexin system seems to play an additional modulatory role, as blocking orexin receptors also inhibits drug-evoked synaptic plasticity (Baimel et al. 2015, Borgland et al. 2006). No plasticity occurs with non-addictive psychoactive substances such as carbamazepine or fluoxetine (Saal et al. 2003). The plasticity was even observed *ex vivo* a day after optogenetic stimulation for 2h of DA neurons, mimicking the activity typically observed with opioids or nicotine (Brown et al. 2010). Intra VTA application of a D1R-antagonist blocked the induction of this optogenetically driven plasticity, in line with a VTA-autonomous process, just as with addictive drugs. Strong DA neuron stimulation is therefore sufficient to elicit the switch of AMPA and NMDARs observed with addictive drugs.

The VTA is also the locus for plasticity in inhibitory circuits with opposing effects on DA neuron activity. First VTA GABA neurons are the preferential target of inhibitory afferents from D1R-MSNs. These afferents enhance their release probability upon cocaine exposure (five daily injections, (Bocklisch et al. 2013)) causing a disinhibition of DA neurons, which may play an important role in the progression of the plasticity to more dorsal parts of the striatum (Everitt & Robbins 2013).

Conversely, VTA GABA neurons (particularly those located in the tail of the VTA or rostromedial tegmentum, RMTg (Jhou et al. 2009)) receive inputs from glutamate neurons of the LHb. These cells are known to encode aversive stimuli (Matsumoto & Hikosaka 2009, Proulx et al. 2014). Cocaine exposure potentiates the LHb-VTA GABA neuron projection (Maroteaux & Mameli 2012) by insertion of additional AMPA receptors and increased intrinsic excitability of the cell bodies (Jhou et al. 2013, Meye et al. 2015). This plasticity may counteract the potentiation of direct excitatory afferents, as the net effect is an enhanced inhibition of DA neurons, which may contribute to aversive affect during withdrawal.

Delayed plasticity in the NAc

Drug-evoked synaptic plasticity also occurs at excitatory afferents onto medium spiny neurons (MSNs) of the NAc. Two elements are important in this context. First, while in the NAc drug-evoked plasticity can be detected a day after the end of a chronic drug exposure, it evolves during the first couple of weeks after withdrawal (Thomas et al. 2001). Most studies focus on this consolidated form,

which coincides with specific drug-adaptive behavior (see below). Second, there are fundamental differences between the two major classes of MSNs of the NAc, the ones that express D1 receptors and those that express D2Rs. Drug-evoked synaptic plasticity in the two populations follows distinct induction rules, contrasting molecular expression mechanisms and opposing functional consequences.

Initial studies applied five injections of cocaine to find a decrease of the A/N ratio and an occlusion of the induction of LTD in acute slices of the NAc a day after the last injection (Thomas et al. 2001). Within two weeks this situation reversed into an higher than normal A/N ratio (Kourrich et al. 2007). At this stage LTD was enhanced while LTP was occluded (Thomas et al. 2001). Moreover, a challenge dose of cocaine at the end of the withdrawal period re-established the low A/N ratio. In other words, exposure to several injections to cocaine leads to a depression of synaptic transmission that reverses into a potentiation within a couple of weeks, but decays within hours if cocaine is reapplied. This sequence of events can also be retraced with biochemical assays quantifying the pool of receptors on the membrane surface (Wolf & Ferrario 2010) confirming a postsynaptic expression mechanism.

The initial depression of transmission is associated with the appearance of many NMDAR-only, therefore silent synapses, which are then gradually transformed into functional units during the withdrawal period (Brown et al. 2011, Lee et al. 2013). Much biochemical evidence indicates that the concomitant activation of D1R and NMDARs engages a signaling cascade that, through the MAPK/extracellular-signal regulated kinase (ERK), supports protein translation and the potentiation of the EPSC (Pascoli et al. 2011). In agreement with this idea, a stimulation protocol that efficiently induces LTP in acute NAc brain slices also activates ERK and applying an ERK inhibitor blocks LTP in the NAc (Pascoli et al. 2012).

Like the VTA, there is good evidence for CP-AMPARs in neurons of the NAc following drug exposure. While it has been claimed that CP-AMPARs only appear when cocaine is self-administered (Conrad et al. 2008, Wolf & Tseng 2012), other studies find CP-AMPARs also after non-contingent (i.e. experimenter administered) drug exposure (Boudreau et al. 2007, Mameli et al. 2009). The application protocol and the cocaine dose seem to play a role in determining which neurons undergo plasticity (**Figure 2**). A recent study suggests that doses up to 0.75 mg/kg per injection in mice selectively induce the plasticity in D1R-MSNs, while higher doses also recruit D2R-MSNs (Terrier et al. 2015). The induction mechanism for the insertion of GluA2-lacking AMPARs in D2R-MSNs has not been investigated, but obviously are not driven by the D1R as described above.

For almost all experimental work on drug-evoked synaptic plasticity in the NAc cocaine was used and but similar adaptations also occur with morphine (REF Thomas PNAS). Moreover, 12 days of optogenetic self-stimulation of VTA DA neurons elicits a synaptic plasticity in D1R-MSNs that is indistinguishable from changes observed after cocaine self-administration (Pascoli et al. 2015), suggesting that strong stimulation of the mesolimbic DA system is ultimately the cause also of the plasticity in the NAc.

mGluR1-LTD to reverse drug-evoked synaptic plasticity

In both the VTA and NAc, metabotropic glutamate receptors are responsible for the removal of CP-AMPARs (Bellone & Lüscher 2006, McCutcheon et al. 2011). Owing to their location at the periphery of the postsynaptic density, activation requires trains of action potentials at frequencies above 10 Hz, such that glutamate transients in the synaptic cleft can reach the metabotropic receptors. The plasticity induced by mGluR1 activation causes a depression of the AMPA-current as high conductive CP-AMPARs are replaced by low conductive CI-AMPARs. The signaling involves mToR and protein synthesis, most likely from prefabricated mRNA, among which some code for the immediate early gene *Arc* and the GluA2 subunit (Mameli et al. 2007, Waung et al. 2008).

In the slice preparation, as well as *in vivo*, positive allosteric modulators (PAMs) can be used to facilitate this reversal process and, at least for the VTA, there is good evidence that mGluR1 activation is the endogenous mechanism to limit the duration of the expression of cocaine-evoked

synaptic plasticity (Mameli et al. 2009). Any deficit of mGluR1 function, be it by pharmacological inhibition or genetic alterations, may make the cocaine-evoked plasticity more permanent. Recent evidence also suggests that the surface expression of mGluR1 receptors may be down-regulated by sustained exposure to cocaine (Scheyer et al. 2014).

Changes in cortical excitability

Drug-evoked plasticity in cortical areas may also depend on D1R signaling where several investigators report changes in excitability of layer V pyramidal cells (some of which project to the NAc) (Buchta & Riegel 2015). For example, input-output curves in slices from animals that were exposed to cocaine are altered reflecting a reduced excitability (Chen et al. 2013). Neither the molecular induction and expression mechanism nor the *in vivo* correlate are known, but the excitability changes are believed to drive plasticity at the target of the projection in the NAc. Major differences seem to exist between the mPFC (hypoexcitability) and the OFC (hyperexcitability) and even within the mPFC (infralimbic versus prelimbic parts(Kalivas et al. 2005, Peters et al. 2008)). These changes in excitability are of particular interest, because several studies (Chen et al. 2013, Kasanetz et al. 2012, Pascoli et al. 2015) suggest that the extent of plasticity may be bi-modally distributed in the experimental population and reflect the resistance to punishment when self-administering cocaine (see below).

REMODELLING CIRCUITS WITH DRUGS

A prerequisite to elucidate the functional consequences of the various forms of drug-evoked synaptic plasticity is the identification of the connection that has been modified. Recent functional tracing methods, and above all optogenetic projection targeting, have allowed decisive progress in dissecting the behaviorally relevant circuitry (**Figure 3**).

In the VTA, by targeting channelrhodopsin to specifit inputs onto DA neurons, it was shown that that cocaine primarily potentiates inputs from the brain stem, notably the laterodorsal tegmentum (Lammel et al. 2012). In contrast, inputs from the mPFC remain largely unchanged.

In the NAc, MSNs are the site of convergence of several afferents that undergo cocaine-evoked synaptic plasticity. For example, after withdrawal from cocaine SA (short access, low dose), the input from the ventral Hippocampus (vHipp) onto D1R-MSNs becomes potentiated by the insertion of CI-AMPARs (Pascoli et al. 2014). In contrast, EPSCs elicited by stimulation of afferents from the mPFC become rectifying, i.e. CP-AMPA receptors appear at different synapses on the same dendrite. Finally, afferents from the BLA to D1R-MSNs remain unchanged unless rodents are allowed extended access to a higher dose of cocaine, at which point CP-AMPARs start to appear also at BLA synapses onto D2R-MSNs (Terrier et al. 2015).

Another aspect that remains only partially understood is the possible hierarchical organization of drug-evoked synaptic plasticity throughout the mesolimbic system. There is evidence that the potentiation at excitatory afferents in the NAc only occurs if the VTA afferent remains potentiated for more than a week (Mameli et al. 2009). For example, when a positive allosteric modulator (PAM) of mGluR1 was used to quickly reverse plasticity in the VTA (see above), even several injections of cocaine failed to cause plasticity in the NAc. The signals governing the march of plasticity from the VTA to the NAc remain to be determined.

ESTABLISHING CAUSALITIES: the link to drug-adaptive behavior

Knowledge of the molecular mechanisms underpinning specific forms of drug-evoked synaptic plasticity, together with the anatomical identification of the relevant connections has enabled the design of specific reversal approaches. The goal of this work is to establish links of causality between drug-evoked synaptic plasticity at identified synapses and drug-adaptive behaviors. The blue print for these experiments (Lüscher 2013) therefore starts with the *ex vivo* characterization of the drug-evoked synaptic plasticity, followed by the establishment of a reversal protocol that is validated first

in the slice and then applied *in vivo* to monitor the effect on the drug-adaptive behavior. The reversal protocol can be pharmacological, or a more specific optogenetic stimulation at a defined input. In both cases the removal of CP-AMPARs by activation of the mGluR1 has proved particularly powerful.

Pharmacological approaches

In the VTA, systemic application of a mGluR1 PAM efficiently restores baseline transmission by driving the synthesis of CI-AMPARs (Mameli et al. 2007). The behavioral impact of the durg-evoked synaptic plasticity is less clear. Most drug-adaptive behaviors with a similar time course remain unaffected, including locomotor sensitization and conditioned place preference. Mice where NMDA receptors were selectively abolished on VTA DA neurons (and thus the cocaine-evoked plasticity in these cells failed to induce) normally self-administer cocaine, but have a reduced cue-associated seeking behavior when tested weeks later (Engblom et al. 2008).

This temporal dissociation between plasticity that appears in the VTA within hours and the associated behavior, which manifests weeks later, suggests that the synaptic changes in the VTA may be merely a permissive metaplasticity (Creed & Lüscher 2013). In other words, the appearance of CP-AMPARs puts VTA DA neurons in a different state that eventually allows for changes in the NAc to occur (Mameli et al. 2009). This idea is in line with the concept of a teaching signal function of DA neurons that stems from the temporal difference learning model (Keiflin & Janak 2015) discussed above. This model, while highly appealing, is not fully tested and recent systematic recordings in VTA neurons indicates a high degree of variability in the activation pattern of DA neurons (Cohen et al. 2012). Moreover some drug-adaptive behavior may occur independently of plasticity in the VTA. For example in GluN1-KO mice conditional for DA neurons, locomotor sensitization induced by cocaine is normal, which, as we will see, has been linked to plasticity in the NAc (Engblom et al. 2008).

The strongest links of causality have been established between cocaine-evoked synaptic plasticity in the NAc and two froms of drug-adaptive behavior, cue-associated drug seeking and incubation of craving. For the latter, infusion of naspm (inhibitor of GluA2-lacking AMPARs) directly into the NAc reduces the increase of lever pressing typically observed during the time of withdrawal (Conrad et al. 2008). Similarly, boosting mGluR1 function with a locally applied mGluR1 PAM again reduces cue-associated seeking and incubation of craving (Loweth et al. 2014)

Optogenetic approaches

Optogenetic projection targeting to induce LTD and thus reverse cocaine-evoked synaptic plasticity was used to restore baseline transmission even more selectively. The first study implementing this approach looked at locomotor sensitization and found that a NMDAR-dependent LTD was sufficient to depotentiate inputs from the mPFC to the NAc and erase this form of drug-adaptive behavior (Pascoli et al. 2012). A similar approach applied to downregulate CP-AMPARs at amygdala-to-NAc synapses to re-silence synapses after prolonged withdrawal attenuated incubation of cocaine craving (Ma et al. 2014). In the latter case, a stimulation protocol was chosen that efficiently activated mGluR1.

Both NMDAR-LTD and mGluR-LTD can be efficient to reverse individual components of drug-adaptive behaviors. Owing to the higher stimulation frequency (> 10 Hz leading to spill over, see above) mGluR1 LTD also has a heterosynaptic component (Lüscher & Huber 2010). For example, a 12 Hz protocol applied to the vHipp to NAc input can remove CP-AMPARs at the mPFC to NAc input. In contrast, 1 Hz-evoked NMDAR-LTD applied at the same input removes CI-AMPARS only at this input (homosynaptic effect). By exploiting these protocols in mice after withdrawal from cocaine self-administration, it has been possible to deconstruct cue-associated seeking behavior (Pascoli et al. 2014). When cocaine-evoked plasticity was selectively reversed at the mPFC input, mice still showed a strong seeking behavior but were unable to predict the action outcome as they pressed the active (previously cocaine-associated lever) or the inactive lever (a lever never associated with cocaine infusions) without distinction. Conversely, reversal of the vHipp input left lever discrimination intact, but reduced the number of presses on the active lever, a reflection of the

reduced seeking vigor. Normalizing transmission at both inputs erased seeking behavior. Importantly, in this study that used a short access session to low doses of cocaine, no synaptic changes were observed at the BLA input and mice did not show incubation of craving (defined as an increase in drug seeking during withdrawal).

Following on from drug effects, optogenetic DA neuron self-stimulation leads not only to reinforcement, but also to cue-associated stimulation seeking and is sufficient to induce resistance to punishment in a fraction of mice (Pascoli et al. 2015). This fraction (65-75%) was substantially higher than what is typically observed with cocaine (20-30% depending on the study). This indicates that VTA DA neuron self-stimulation is not only sufficient to induce addiction (at least a simple form of the disease in rodents), but it does so more efficiently than the most addictive drugs. The non-specific nature of the pharmacological activation (e.g. cocaine also increases other monoamines than DA) may in some way actually be protective.

In this study, resistance to punishment was found to segregate with enhanced excitability of pyramidal neurons of the OFC and chemogenetic modulation of OFC excitability affected resistance to punishment, thereby establishing causality. These findings complement a study where optogenetic activation of the prelimbic cortex inhibited cocaine seeking in resistant rats, while inhibition of the same area had the converse effect (Chen et al. 2013). As argued above, research on the molecular and cellular mechanisms of cortical plasticity is still in its infancy and much additional research will be needed to integrate these circuits in the emerging model. For example, OFC activity is inversely correlated with habitual learning (Gremel & Costa 2013a,b), which raises the question whether habitual learning and compulsive drug use are sequential steps in the progression to addiction. This question is of particular relevance also in the context of the proposed shift from ventro-medial to dorso-lateral stratal circuits as compulsive drug consumption takes over (Everitt & Robbins 2013). The synaptic mechanisms governing the recruitment of more and more dorsal loops remain elusive, but are likely to include plasticity of GABA transmission (Bocklisch et al. 2013) or modulation by cholinergic signaling covered elsewhere (Threlfell & Cragg 2011).

In models of averse effects observed during acute withdrawal,the behavioral correlate of enhanced inhibition onto VTA DA neurons may be a depression-like state, as a dominant negative peptide inhibiting the insertion of GluA1 and thus preventing the potentiation from the LHb to the RmTg significantly abolishes enhanced immobility in the forced swim test, a marker of depression-like behavior typically observed during cocaine withdrawal (Meye et al. 2015).

Taken together these experiments provide compelling evidence for a link of causality between drug-evoked synaptic plasticity and drug-adaptive behavior. Current studies now aim at characterizing the ensuing alteration in neural activity, starting with distinct populations in the NAc and cortical areas. Interestingly using PET imaging, a positive correlation between craving and OFC activity has been established and the projection to the NAc has been implicated in the compulsive component of consummatory behavior (Volkow et al. 2005). In contrast, most of the preclinical literature describes drug-adaptive changes that occur in all animals. The exception is of excitability changes in cortex that are only seen in rodents resistant to punishment, thus coming closest a simple definition of actual addiction.

THERAPEUTIC IMPLICATIONS : optogentically inspired DBS

Given the power of optogenetic reversal protocols to erase drug-adaptive behavior, one might be tempted to explore translational aspects of this approach. Wouldn't it be great to correct pathological circuit function, such that an addict can again control his or her decisions and lead a normal life? This may eventually become possible, yet, in our opinion, not in in the near future (Lüthi & Lüscher 2014). There are many obstacles, such as the need for cell-type specific targeting, the failure to stably express opsins for the intended duration of the therapy (typically years), or the threat of long-term toxicity. Much development will be required to overcome these limitations. There might however be a window in which to take advantage of optogenetics for the development of novel protocols of established circuit therapies. Two techniques come to mind, deep brain stimulation (DBS) and

transcranial magnetic stimulation (TMS). Compared to optogenetics, electrical and magnetic stimulation is however non-specific and the sought after effects may be masked by activation of other neural structures and projections.

Characterizing pathological circuit function with optogenetics, with the goal to design blueprints for manipulations aiming at restoring normal circuit function could constitute an alternate approach (Lüscher 2013). The initial step consists of reversing the pathological behavior, still with optogenetics, in preclinical disease models. Next, the challenge consists of establishing ways to emulate the optogenetic protocols with DBS, still in an animal model. The goal is to obtain a similar effect on behavior while validating the underlying mechanism, ideally also in non-human primates. Then, and only then, clinical trials could be envisioned that start with tests for safety and efficacy. In other words, optogenetically inspired DBS may be the 'hic et nunc' translation of optogenetics.

Only a few studies have been published that may provide proof of principle for this approach. For example, a novel DBS protocol to reverse locomotor sensitization to cocaine (Creed et al. 2015). As discussed above, this behavior is driven by a potentiation of excitatory afferents onto D1R-MSNs in the NAc. Optogenetic reversal through a mGluR1-dependant LTD mechanism (10-15 Hz stimulation for 10 minutes) erases the drug-adaptive behavior (Pascoli et al. 2012). Initial attempts with DBS in the NAc in mice applying a similar stimulation parameter (10-15 Hz for 10 minutes the day before the testing) however failed to reverse locomotor sensitization and classical DBS (130 Hz continuous stimulation) only had a transient, non-specific effect. The *ex vivo* analysis in the slice preparation showed that neither of the DBS protocols were able to induce the mGluR-LTD required to restore baseline transmission (**Figure 4**). This is not surprising, because the non-specific electrical stimulation was also driving dopamine release from midbrain afferents that, when activating D1R, inhibited the signaling cascade required to express mGluR-LTD (Shen et al. 2008). This scenario was confirmed by the rescue of mGluR-LTD in the presence of a D1R antagonist (SCH29930 or SCH31166) and the ensuing erasure of the locomotor sensitization. The D1R antagonist paired with short low-frequency DBS protocols was efficient when directly applied into the NAc, as well as when given systemically, demonstrating the locus of action and suggesting a translational approach, respectively. This optogenetically inspired DBS protocol fundamentally differs from currently used clinical DBS protocols as they use intermittent stimulation, a different frequency and are paired with a pharmacological adjuvant to enhance specificity.

It is likely that similar protocols can be established for addiction by targeting other nodes of the disease-relevant circuitry (in this regard the superficial cortical areas may be a much better targets for optogenetically inspired TMS protocols, as suggested by a recent pilot study, Terraneo et al. 2015). A comprehensive characterization of adaptive synaptic changes may reveal additional targets where circuit-breaking manipulations may be successful.

CONCLUSIONS AND PERSPECTIVES

In summary, the circuit model of drug addiction proposed here is based on much experimental evidence collected in rodents, taking advantage of simplified, yet robust behavioral models for this brain disease. Various forms of drug-evoked synaptic plasticity represent the key mechanism underlying altered circuit function and eventually drug-adaptive behavior. The earliest forms are observed at the origin of the mesolimbic DA system, in dopamine neurons of the VTA, but with repetitive exposure then spread to the NAc. A commonality of many forms of drug-evoked synaptic plasticity is the appearance of calcium-permeable AMPA receptors, which may shape altered circuit function by changing the rules for the induction of experience-dependent plasticity. The identification of the disease-relevant changes in circuits has become possible with enhanced techniques of modern neuroscience, above all optogenetics, Ongoing studies focus on the determinants of individual vulnerability. Epigenetic mechanisms are likely to play an important in the molecular mechanisms underlying drug-evoked synaptic plasticity or environmental factors that increase individual vulnerability (e.g. stress). Knowledge about circuit adaptations in addiction also allows probing of novel therapeutic approaches. Over the last few years, optogenetic strategies have thus emerged that treat drug-adaptive behavior in animals based on rational predictions. While exclusively applicable in animal models, they may lead the way for circuit manipulations in humans

using DBS or TMS, a strategy we call optogenetically inspired DBS and TMS, which may also extend to additional indications.

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Figures:

Figure 1: Overarching hypothesis of DA evoked circuit adaptations leading to addiction. Schematics of the mesolimbic dopamine (DA) system with its origin in the ventral tegmental area and two primary projection sites, the nucleus accumbens and the medial prefrontal cortex. Addictive drugs converge onto a minimally required circuit that may explain an increase in DA concentations through three distinct cellular mechanisms. Nicotine can directly depolarize DA neurons, while the psychostimulants cocaine, ecstasy and amphetamine interfere with DA reuptake mechanisms. Note that this mechanism also increases DA in the VTA, because these neurons also release the transmitter from their dendrites. A third group including opioids, gamma hydroxyl-butyrate (GHB), cannabis and benzodiazepines have a disinhibitory effect, which is the result of the presynaptic release probability in combination with the hyperpolarization of VTA GABA neurons. This minimally required circuit element is also modulated by afferent circuits (not shown) and subject to acute adaptations (e.g. desensitization of nicotine receptors).

Figure 2: Synapse-specific plasticity in NAc. Contrasting expression mechanisms of drug-evoked synaptic plasticity as a function of the projection. Note that the exposure to high concentrations of cocaine leads to insertion of GluA2-lacking AMPARs in both D1R and D2R-MSNs, albeit at distinct inputs.

Figure 3: Disease-relevant circuits. Major connections undergoing drug-evoked synaptic plasticity and associated drug-adaptive behavior on a sagittal section of the brain. OFC: Orbitofrontal cortex, mpfc: medial prefrontal cortex, NAc: nucleus accumbens, BLA: basolateral amygdala, VP: ventral pallidum, vHippo: ventral Hippocampus, LHb: lateral habenula, RMTg: rostro medial tegmentum, LDT: laterodorsal tegmentum, VTA: ventral tegmental area. Note that most of the connections where drug-evoked synaptic plasticity was characterized are glutamatergic, with the exception of the inhibitory afferents from the NAc onto VTA GABA neurons. Red: Dopamine, Blue: Glutamate, Green: GABA.

Figure 4: Optogenetically inspired DBS. Optogenetic stimulation causes selective release of transmitter from glutamate afferents (blue). With strong stimulation glutamate reaches the perisynaptically located mGluR1s, which trigger an intracellular signaling cascade eventually removing GluA2-lacking AMPARs (green) previously inserted by cocaine exposure. Canonical DBS fails to trigger this process because the electrodes also stimulate DA afferents (red). As a consequence, D1R signaling inhibits the expression of mGluR1-depotentiation. Optogenetically inspired DBS associates electrical stimulation with a D1R antagonist (e.g. SCH23390, red diamonds) thus blocking the D1R signaling and rescuing mGluR1-depotentiation the synapse.